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Nucleic acid-based medicines: innovation and regulatory challenges

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Introduction

Oligonucleotides (ONs) are made of RNA or DNA strands that interact with human natural RNA or proteins through different pathways. According to the nucleic acid structure, length, and molecular target, 4 main classes of ON-based medicinal products (ONMs) can be currently identified: antisense oligonucleotides (ASOs), small-interfering RNA (siRNAs), aptamers and messenger RNAs (mRNAs). When delivered to the cell cytosol, mRNAs can induce the translation of proteins and, therefore, are generally preferred for producing vaccines. Unlike mRNAs, other ONs cannot directly translate proteins, but can module existing pathways of their expression. ASOs are single-stranded ONs (≈12-25 nucleotides) that bind pre-mRNA or mRNA [1]. siRNAs are double-stranded ONs (≈20-24 nucleotides) able to target and bind cytoplasmatic RNAs to inhibit translation of pathogenic proteins. Instead, aptamers are single-stranded ONs characterized by a well-defined 3D structure able to specifically bind to and inhibit proteins.

This work aims to analyze the features of ONMs authorized by EMA and FDA and discuss the peculiarities of the regulatory pathways used to reach the market.

Methods

Data about the ONMs' regulatory history were collected through both EMA website (https://www.ema.europa.eu/en) and the FDA website (https://www.fda.gov/). All products that have been authorized, withdrawn, and refused till October 2023 were included. Moreover, the orphan status of EU-authorized medicines was checked on the "Community Register of orphan medicinal products", and for US-authorized ones on FDA website. The ATC codes have been detected from SPCs and have been confirmed by searching them in the WHO website (https://www.whocc.no/) [2].

Results

21 ONMs have been recorded in EMA/FDA websites. The majority of ONMs (67%) are classified as **orphan drugs** by both EMA and FDA. Grouping products by ONM classes, most of them are ASOs (52%), followed by siRNAs (28.6%). From 1998, 11 **ASOs** have been examined by both EMA and FDA; 3 of them are currently authorized in Europe and 7 in the US. 3 ASOs have been authorized by only a Regulatory Agency, since the other refused them due to safety concerns or insufficient data. 2 products were withdrawn for commercial reasons in the US and/or in the EU. Only one aptamer (Izervay®) is on the market in the US, since the Macugen®, authorized in both the US (2004) and the EU (2006), was withdrawn for commercial reasons in 2011. As far as **siRNAs**, following the first one (Onpattro®) approved by FDA in 2018, 5 additional products have been authorized in the last years in both US and EU. Finally, mRNAs are available only as COVID-19 vaccines, which were approved at the end of 2020 in both US and EU.

Therapeutic features

As shown in *Figure 1*, 23.8% of medicines are indicated for disorders of the musculo-skeletal system (M09). 19% is associated to the nervous system (N07) and 14.3% is represented by lipid modifying agents (cardiovascular system, C10). 9.5% of products are used for diseases related to alimentary tract and metabolism (A16); the same percentage has been noticed also for ophthalmological pathologies (S01) and anti-infective for systemic use (J07). Only one medicine is used as an antineoplastic agent (L01). The ATC codes have not been assigned yet in 2 cases: one for primary hypoxaluria type 1 and one for geographic atrophy secondary to age-related macular degeneration.

API and Formulative features

All ASOs, siRNAs and aptamers have been considered, from a regulatory point of view, as **small molecules** since they are chemically synthesized using solid phase methods. Based on chemical modifications of nucleotide sugar-phosphate backbone, marketed ASOs can be sub-classified in *phosphorothioate oligonucleotide* (PSO) and *phosphorodiamidate morpholino oligomer* (PMO) (*Table 1*).

Instead, the mRNAs are obtained by in vitro transcription (IVT) starting from linear DNA; consequently, they are generally classified as **biological** medicinal products.

Focusing on the delivery platform, only 3 out of 21 ONMs are formulated with **lipid nanoparticles:** in the case of the two mRNA vaccines, the use of nanosystems permitted to preserve the loaded ONs for degradation; in the case of Onpattro®, they have also facilitated the delivery to the target site of action, the liver.

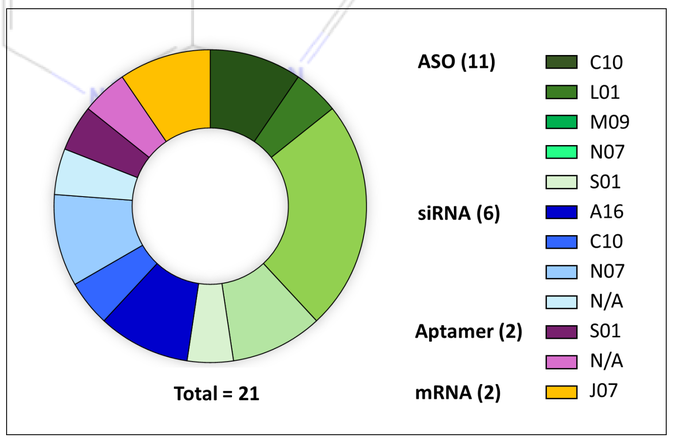

Figure 1. Overall ONMs authorized by EMA/FDA grouped by ON class and ATC code; N/A: not available.

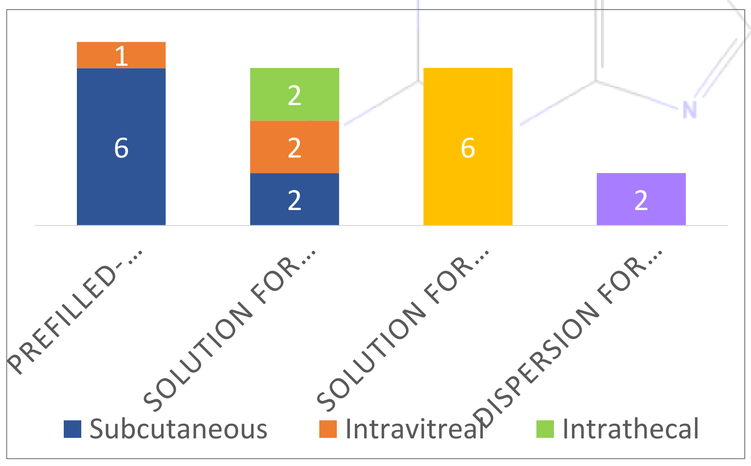

Figure 2. Number of ONMs regarding pharmaceutical forms and routes of administration.

Taking into consideration the pharmaceutical forms, most ONMs (33%) are solutions manufactured as **pre-filled syringes** for subcutaneous administration. Many are solutions for injection (29%) and infusion (29%) and only mRNA vaccines are dispersions for injection (10%). In *Figure 2*, the pharmaceutical forms are correlated to the different routes of administration.

Medicine	API	Date of first MA (US/EU)	Sugar-phosphate backbone
Amondys	Casimersen	25/02/2021 (US)	PMO
Exondys	Eteplirsen	19/09/2016 (US)	PMO
Kynamro	Mipomersen	29/01/2013 (US)	PSO
Qalsody	Tofersen	25/04/2023 (US)	PSO
Spinraza	Nusinersen	23/12/2016 (US)	PSO, 2nd generation
Tegsedi	Inotersen	06/07/2018 (EU)	PSO, 2nd generation
Viltepso	Viltolarsen	12/08/2020 (US)	PMO
Vitravene	Fomivirsen	26/08/1998 (US)	PSO
Vyondys	Golodirsen	12/12/2019 (US)	PMO
Waylivra	Volanesorsen	03/05/2019 (EU)	PSO, 2nd generation

Table 1: Overall ASOs authorized by EMA or FDA.

Discussion and Conclusion

ONMs are a very heterogeneous class of medicines due to the different mechanism of action, therapeutic indications, API production methods, and formulative features. Despite the pharmaceutical interest in ONMs, both EMA and FDA are still facing **regulatory challenges** in providing requirements and standards for such novel therapeutic classes. This includes criticisms on assessing quality aspects related to the use of nanosystems as ONs' carriers [3]. Part of the problem is the lack of a regulatory consensus on a harmonized classification of ONMs [4]. Unlike the US where ONMs are managed as non-biological drugs, the recent EC proposal of **Reform of the EU pharmaceutical legislation** seems to be aimed at classifying all ONMs as ATMPs [5]. The consequent conceptual misalignments between the EMA and FDA might result in unneeded regulatory barriers between the EU and the US. Due to the heterogenicity and innovative nature of ONMs, a detailed legislative classification, based on the nature of the API source or production, may be counterproductive. The assessment of benefit/risk balance of ONMs, and therefore the data provided by applicant, should be primarily grounded both on their peculiar quality aspects related to the manufacturing process and on their efficacy and safety profiles related to mechanism of action.

References

1) Quemener, A.M., et al. The powerful world of antisense oligonucleotides: From bench to bedside. Wiley Interdiscip Rev RNA, 11, e1594 (2020).
2) WHO. International Nonproprietary Names (INN) for biological and biotechnological substances (a review). https://www.who.int/publications/m/item/who-mhp-hps-inn-2022-2 (2022).
3) Musazzi, U.M., et al. Feeding Next-Generation Nanomedicines to Europe: Regulatory and Quality Challenges. Adv. Healthcare Mater. 2301956 (2023).
4) Thakur, S., et al. A perspective on oligonucleotide therapy: Approaches to patient customization. Front. Pharmacol. 13, 1006304 (2022).
5) European Commission (EC). Reform of the EU pharmaceutical legislation. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en (2023)

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